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EDITORIAL COMMENT

Cardiac Troponins

A Tool for a Personalized Medicine Strategy in Stable Coronary Artery Disease?*

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"However beautiful the strategy,
you should occasionally look at the results."
—Sir Winston Churchill (1)

The term *stable coronary artery disease* encompasses a range of patient categories, including patients with classic angina pectoris and those with previous obstructive acute or stable coronary artery disease (CAD) who have been successfully treated. Although stable CAD per definition can be considered a low-risk group compared with patients with acute coronary syndromes (ACS), it is associated with a substantial long-term risk of adverse events (2). Within the overall group of patients with stable CAD, there is considerable variation in risk, and the risk may vary over time on the individual level. Serial prognostic assessment could therefore be of considerable importance as a tool to identify patients who might benefit from appropriate and timely diagnostic evaluation and therapeutic intervention. Equally important, prognostic assessment may be used to identify low-risk patients who may safely be treated conservatively, thus avoiding unnecessary invasive investigations and therapeutic procedures.

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Until recently, measurement of cardiac troponin levels has been almost exclusively performed to diagnose acute ischemic injury in patients with suspected acute myocardial infarction (MI). In parallel with the gradual improvement in analytical performance of assays, progressively lower circulating concentrations of cardiac troponins can be detected with acceptable precision, paving the way for accurate quantification of chronic circulating concentrations in low-risk groups (3). Even within this low-level range, cardiac troponin levels measured by a new generation of sensitive assays have been shown to be robustly associated with the risk of cardiovascular death and heart failure (4–6). Somewhat unexpectedly, the association with MI is weaker and attenuated after adjustment for conventional risk markers (4).

In this issue of the *Journal*, White et al. (7) report data from the biomarker substudy of the LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease) trial, performed in the 1990s (8). The main trial tested the effect of pravastatin 40 mg versus placebo in a large cohort of patients with a history of ACS and was stopped prematurely because of a beneficial effect of the intervention. The current report evaluated the association between baseline cardiac troponin I concentrations and their change during the first year of follow-up and the risk of the composite primary endpoint of death due to cardiovascular causes or nonfatal MI. Moreover, the study examined the potential interaction between cardiac troponin I levels and the effect of the intervention. The results of this well-conducted study confirm and extend previous results, suggesting that the measurement of cardiac troponin levels using contemporary sensitive methods can refine risk prediction among patients with stable CAD. Moreover, the study shed light on some of the yet unanswered questions related to the use of cardiac troponins in this patient group. First, confirming data from the PEACE (Prevention of Events With Angiotensin Converting Enzyme Inhibition) study (4,9), cardiac troponin I, after adjustment for a comprehensive risk marker model, was robustly associated with the incidence of cardiovascular death and heart failure, whereas the association with stroke and nonfatal MI, although nominally statistically significant, was weaker. For the composite primary endpoint of cardiovascular death or nonfatal MI, cardiac troponin I added to the baseline model resulted in a modest but significant net reclassification improvement.

Whether change in cardiac troponins measured with highly sensitive assays provides additional prognostic information to that obtained from baseline measurements alone has previously been assessed in elderly individuals from the general population (6) and patients with chronic systolic heart failure (10). Extending these results, the LIPID investigators demonstrated that in patients with stable CAD, the shift from a lower concentration to higher concentration category is associated with increased risk, independently of baseline levels and other risk markers. Moreover, measurements performed at baseline and after 1 year provided independent prognostic information, suggesting that serial monitoring of cardiac troponin levels reflects dynamic changes in cardiovascular risk.

Do these findings suggest that cardiac troponin measurements should be recommended in the routine follow-up of this large patient group? Although risk

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stratification and knowledge about change in risk may suggest to the clinician that patients with high and increasing risk should be monitored more closely and potentially managed more aggressively than patients with low or decreasing risk, it offers no specific guidance to what therapy will benefit patients. In other words, although it may seem reasonable to refer patients with stable CAD and high and/or increasing troponin concentrations to noninvasive or invasive diagnostic tests and to consider intensifying therapy, it is still unknown whether this strategy will lead to improved patient outcome. Conversely, we lack data demonstrating that it would be safe to withdraw conventionally accepted secondary prevention measures in patients with stable CAD and low and/or decreasing troponin levels.

Use of cardiac troponins as a guide to therapy in a personalized medicine strategy has successfully been demonstrated in ACS, when it was convincingly shown that patients with chest pain with elevated cardiac troponin levels on admission benefited from intensified medical therapy (11) and from an early invasive versus a conservative strategy (12). Conversely, patients with troponin levels within the normal range did not seem to benefit from such intensification of therapy (11,12). These observations have contributed to the routine use of cardiac troponin measurements in patients presenting to the hospital with acute chest pain and suspected acute MI (13), and the use of cardiac troponin levels to guide treatment decisions in ACS represents a preeminent example of a successful personalized medicine strategy within the field of cardiovascular medicine.

Statin therapy is a cornerstone in the management of patients with stable CAD. The hypothesis that risk stratification based on cardiac troponin concentrations can be used to predict the effect of statins, as tested in the LIPID substudy, is interesting, although it can be argued that in the stable CAD setting, chronic elevation of cardiac troponins may preferentially reflect other pathophysiological processes than those primarily affected by the lipid-lowering and pleiotropic effects of statin therapy. In the LIPID trial, treatment with pravastatin was associated with a slight but statistically significant reduction of cardiac troponin I at 1 year. However, the relative treatment effect on clinical outcomes was similar across different categories of cardiac troponin I, and no formal interaction between cardiac troponin I levels and the effect of pravastatin was evident, suggesting no clinically important utility of these biomarkers as a tool for selection of patients who will benefit from statin therapy. The authors observed that higher baseline cardiac troponin levels were associated with a larger absolute benefit from pravastatin, and thus, the number needed to treat was less in patients with high than in those with low baseline levels. Given that higher troponin I levels were associated with higher absolute risk and the relative risk reduction was similar across troponin categories, this observation is not surprising and just reflects the inverse association between absolute risk reduction and number needed to treat.

A variety of potential causes of cardiac troponin elevation could account for the observed association with cardiovascular risk. Thus, it is not clear that statin therapy would be the optimal intervention to test the hypothesis that troponins can be used in a personalized medicine strategy to identify patients likely to benefit from therapy. Recent data suggest that mild, chronic elevation of cardiac troponins is more strongly associated with cardiac anatomy and function than with the extent of CAD (5). Moreover, the combination of left ventricular hypertrophy and elevated cardiac troponins seems to identify a particularly malignant phenotype (14). This suggests that interventions aimed at reducing myocardial strain and reversing cardiomyocyte hypertrophy may be more effective at reducing cardiac troponin levels than statins, and it is conceivable that cardiac troponins would be predictive of the effect of such interventions. Still, retrospective data from the PEACE study failed to show any interaction between cardiac troponin T levels at baseline and the benefit of the angiotensin-converting enzyme inhibitor trandolapril in low-risk patients with stable CAD (4). Thus, despite the important finding of the LIPID study that serial troponin measurement can refine risk stratification in stable CAD, the clinical benefit of the theoretically beautiful strategy of using cardiac troponins as a management criterion in this patient group remains unproven. Prospectively and intelligently designed trials testing interventions that both are pathophysiologically linked to cardiac troponin production and are effective in reducing risk associated with such pathophysiology in stable CAD will be required to definitively answer the decisive question of whether cardiac troponin measurements can translate into improved patient management.

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